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Pregnancy Outcome Following Exposure to Topical Retinoids: A Multicenter Prospective Study

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Concerns have been raised about the use of topical retinoids since the publication of isolated cases of characteristic retinoid embryopathy, originally described after oral use. A collaborative study of the European Network of Teratology Information Services was carried out to evaluate the rate of congenital malformations following first-trimester topical retinoid exposure. A population of 235 exposed pregnant women was compared with 444 controls. No significant differences were observed between groups with regard to the rates of spontaneous abortion (odds ratio [95% confidence interval], 1.5 [0.8-2.7]), minor birth defects (1.3 [0.4-3.7]), and major birth defects (1.8 [0.6-5.4]). No child showed features of retinoid embryopathy. The rate of elective termination in the exposed group was increased 3-fold (3.4 [1.5-7.8]). In conclusion, these results do not suggest an increased risk of retinoid embryopathy. However, according to current knowledge, topical retinoids cannot be advised for use during pregnancy because their risk/benefit ratio remains questionable.

Keywords: *Clinical pharmacology; drug information; pregnancy; topical retinoid; birth defect*
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Human teratogenicity of oral retinoids was clearly established by the mid-1980s. Their use in pregnancy both increases the risk for spontaneous abortion and leads to the characteristic retinoid embryopathy, comprising anomalies of the ears, facial and palate defects, micrognathia, cardiovascular defects, and developmental impairment of the thymus and the central nervous system.[1] Mental deficiencies have also been reported in children with no notable physical anomaly exposed in utero to isotretinoin.[2] Consequently, retinoids are considered to date the most serious teratogenic threat since thalidomide, and pregnancy prevention programs are implemented worldwide (eg, iPLEDGE)[3] to reduce inadvertent exposures.[4]

Topical retinoids are used to treat a variety of dermatologic conditions, from acne to sun damage. They are also ingredients commonly found in *cosmeceuticals*, making women of childbearing age prime candidates for their use. Human and animal data argue against plausible teratogenicity because of minimal systemic absorption (values measured from undetectable to a small fraction of the dose, not exceeding endogenous levels) after topical application in the absence of significant skin damage.[5-10] However, despite such reassuring considerations, several published case reports described infants exposed in utero

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to topical tretinoin who exhibited structural abnormalities consistent with retinoic acid embryopathy.[11-15] In contrast, 3 small epidemiological studies[16-18] did not identify a significantly increased risk associated with topical tretinoin, for either retinoic acid embryopathy or major structural defects overall. One case report on adapalene and 1 epidemiological study involving tretinoin did not indicate an increased risk of developmental disorders.[19,20] Data on the safety of several topical retinoids (motretinide, tazarotene, adapalene) in pregnancy are still missing.

According to current knowledge, health care practitioners remain reluctant to rule out a potential for low-level teratogenicity of topical retinoids.[21] This might consequently foster maternal fear and lead to termination of healthy and otherwise wanted pregnancies even though the risk of malformations from topical retinoid exposure is not considered significantly increased by many teratology information specialists.[22]

The purpose of this study was to assess the frequency of a spectrum of adverse birth outcomes associated with first-trimester exposure to topical retinoids, to enrich rather scarce human data available to date. We compared the overall prevalence of major or minor birth defects at birth, the rate of spontaneous abortion, and the rate of elective termination of pregnancy after first-trimester exposure to topical retinoids with the baseline prevalence in pregnancies exposed to no known teratogen.

METHOD

Our prospective, controlled, multicenter, observational study involved 11 teratology information services (TIS). It enrolled pregnant women exposed during the first trimester to topical retinoids, and these women or their doctors contacted a TIS to seek advice between 1992 and 2006. Patients were asked for consent to further gather follow-up information. The 11 TIS centers are members of the European Network of Teratology Information Services (ENTIS), an organization of services providing evidence-based information on the safety and risks associated with exposure to drugs during pregnancy and breastfeeding, using similar methodology. Furthermore, ENTIS members document prospectively the course of exposed pregnancies to study drug safety with respect to developmental toxicity.[23] The study was approved by the ENTIS investigational committee.

Women were exposed to adapalene, tretinoin, isotretinoin, motretinide, retinol, or tazarotene; if more than 1 topical retinoid was used, exposure was classified as a combination. The exposed group was compared with an ENTIS control group of women who had used drugs known to be nonteratogenic during pregnancy (eg, paracetamol, labetalol, meclozine, loratadine, salbutamol, ranitidine, amoxicillin, omeprazol, budesonide inhalation). Controls were enrolled in the same TIS/country, in a similar timeframe. Similar documentation and follow-up methodology were used in both the exposed pregnancies and the controls. To strengthen the power of our study, a 1:2 ratio was used between the size of the cohort exposed to topical retinoids and of the control group. Each case of topical retinoid exposure was to be matched with 2 controls of the same center for maternal age and gestational age at the time of the call.

Using structured questionnaires or phone interviews, exposure details (drug, time of exposure, dose), concomitant medication, maternal demographics, and medical and obstetric histories were collected prospectively for each pregnant woman (ie, topical retinoid use or control group).[24]

After the predicted date of birth, follow-up information was requested through structured telephone interviews and/or mailed questionnaires sent to the mothers or physicians. Details on pregnancy outcome, gestational age at delivery, birth weight, congenital anomalies, and neonatal complications were obtained. In most cases, gathering of follow-up data was performed during the neonatal period. Pregnant women considered lost to follow-up were not included in the analysis (overall rate of loss to follow-up in the ENTIS group is known to range from 10% to 40% and is expected to be similar in both groups). A variable was not considered for analysis if more than 30% of the data were missing.

The primary outcome of interest was the rate of major birth defects, defined as having serious medical, surgical, or cosmetic consequences,[25] and minor birth defects with special attention to anomalies indicative of retinoid embryopathy. All reported birth defects in exposed and control newborns were sent to an ENTIS birth defect specialist, who blindly classified them between major and minor. Secondary end points were the rates of live births, spontaneous abortions, pregnancy terminations (elective or therapeutic), stillbirths, premature births (<37 weeks), gestational age at term, and birth weight. Gestational age in the present study is defined as the number of weeks after the last menstrual period.

The proportion of major or minor birth defects, spontaneous abortions, elective or therapeutic abortions, and live births reported in the exposed group

was compared with the control group using a χ^2 test or Fisher exact test when assumptions for χ^2 were not met. In addition, a 95% confidence interval (CI) was defined using odds ratio (OR) calculation for major and minor birth defect rates. All continuous variables of interest, such as gestational age at birth and birth weight, were compared between the exposed and the control groups using the Student *t* test or Wilcoxon test when assumptions for parametric tests were not met. The level of statistical significance was set at $P < .05$ for the primary outcome. For all other outcomes, *P* values were presented only for exploratory comparisons. To assess the impact of heterogeneity among retinoids, we applied an analysis of deviance in the framework of logistic regression analysis for categorical data and an analysis of variance (ANOVA; with error sum of squares) for continuous data.

We used a retrospective power calculation to estimate the minimal detectable difference with the available sample size (ie, estimation of the statistical power of the study to detect an increase in birth defects after topical retinoid exposure). This estimation was performed assuming a significant level ($\alpha = 0.05$) and a type II error rate ($\beta = 0.2$), as well as a baseline incidence as the rate found in the control group (1-tailed test).

The χ^2 test, Student test, Wilcoxon test, logistic regression, ANOVA, and power calculation were performed using STATA version 9.2 (StataCorp, College Station, Texas).

RESULTS

Eleven TIS of the European Network participated in the study. Three centers could not provide controls as requested. The Berlin TIS provided the missing controls for Europe and Zerifin for Israel (Table I). A total of 235 pregnancy outcomes were recorded following exposure to various topical retinoids (tretinoin, n = 143; isotretinoin, n = 52; adapalene, n = 24; retinoic acid, n = 10; motretinide, n = 1; combination, n = 5; Table II), and 444 matched outcomes in controls exposed to drugs considered nonteratogens were collected. Several descriptive variables were not considered for analysis as they comprised more than 30% of missing values (eg, street drug use, detailed concomitant medication, gestity, parity, social status).

Almost all patients treated with topical retinoids were exposed from the beginning of pregnancy, with the treatment having been started before conception.

Table I Teratogen Information Services

	Retinoids (n = 235)	Controls (n = 444)
Servicio de Información Telefónica sobre Teratógenos Español (Madrid, Spain)	19	0
Servizio di Tossicologica Perinatale (Firenze, Italy)	19	21
Beilinson Teratology Information Service (Tel Aviv, Israel)	13	28
Israel Teratogen Information service (Jerusalem, Israel)	27	0
TIS-Helsinki (Finland)	8	16
Centre de Pharmacovigilance (Lyon, France)	26	52
Poison Control Centre (Bergamo, Italy)	6	16
TelefonoRosso (Rome, Italy)	27	56
Drug Consultation Information Center (Zerifin, Israel)	4	64
Swiss Teratogen Information Service (Lausanne, Switzerland)	13	0
Pharmakovigilanz- und Beratungszentrum Embryonaltoxikologie (Berlin, Germany)	73	191

Table II Retinoids Identified

	Retinoids (n = 235)
Tretinoin	143
Isotretinoin	52
Adapalene	24
Retinoic acid	10
Motretinide	1
Combination	5

The mean start time of exposure was 1.8 ± 3.2 gestational weeks. Most pregnant women stopped topical retinoids when pregnancy was confirmed, thus yielding a mean time of exposure of 8.1 ± 5.8 gestational weeks. The most frequent treatment indication was acne (n = 174). Psoriasis, alopecia, bleaching, dermatitis, and cellulitis were less often reported.

Maternal characteristics of patients in the topical retinoids group and the control group are presented in Table III. Except for a slight difference in maternal age, there were no significant differences in any of the maternal characteristics in both groups. Women

Table III Maternal Data

	Retinoids	Controls	*P* Value[a]
Maternal age	222	435	
Median, y [range]	30 [21-42]	32 [17-48]	.0024
<24, No. (%)	25 (11)	36 (8)	
25-30, No. (%)	90 (40)	130 (30)	
31-35, No. (%)	70 (32)	168 (39)	
≥35, No. (%)	37 (17)	101 (23)	
Gestational weeks at call			
Median, wk [range]	7 [3-35]	8 [2-39]	.23
Tobacco use, No. (%)	23 (12)	32 (7)	.14
Alcohol use, No. (%)	10 (5)	13 (3)	.38

a. χ^2/Fisher exact or Student/Wilcoxon tests.

Table IV Pregnancy Outcomes and Newborn Data

	Retinoids	Controls	*P* Value[a]
Live born, No. (%)	200 (85)	410 (92)	
Spontaneous abortion, No. (%)	19 (8)	26 (6)	.19
Elective termination, No. (%)	15 (6)	7 (2)	<.001
Therapeutic termination, No. (%)	1 (<1)	0 (0)	.16
Fetal death, No. (%)	0 (0)	1 (<1)	.65
Gestational age at term			
Mean ± SD, wk	39.4 ± 1.9	39.4 ± 2.1	.43
<37 wk, No. (%)	9 (5)	29 (7)	.32
Birth weight	(n = 192)	(n = 362)	
Mean ± SD, g	3301 ± 495	3324 ± 567	.32
Sex	(n = 193)	(n = 349)	
Male, No. (%)	94 (49)	178 (51)	.55

a. χ^2/Fisher exact or Student/Wilcoxon tests.

in both groups were enrolled in the study at a similar gestational timing, on average at the end of their second month of pregnancy.

Pregnancy and newborn outcomes are detailed in Table IV. A total of 200 live births, 19 spontaneous abortions, 15 elective terminations, 1 therapeutic termination, and no stillbirths were observed in the group exposed to topical retinoids. None of the children showed features of retinoid embryopathy. The mean (SD) gestational age at delivery was 39.4 (1.9) weeks, and mean (SD) birth weight was 3301 (495) g. Pregnancy outcomes in the control group included 410 live births, 26 spontaneous abortions, 7 elective terminations, 0 therapeutic terminations, and 1 stillbirth. The mean (SD) gestational age at delivery was 39.4 (2.1) weeks, and mean (SD) birth weight was 3324 (567) g.

The proportion of mothers who spontaneously aborted or had a therapeutic termination of pregnancy was not significantly different in the topical retinoids group compared with the control group (8% vs 6% for spontaneous abortion: $P = .19$; less than 1% vs 0% for therapeutic termination: $P = .16$). However, women in the exposed group were more likely to undergo elective termination of their pregnancy (6% in the exposed group vs 2% in the control group; $P < .001$). Gestational age at term, as calculated from the first day of the last menstrual period

Table V Birth Defects in Retinoid and Control Group

	Retinoids (n = 235)	Controls (n = 444)	Odds Ratio (95% Confidence Interval)
Major birth defects, No. (%)	8 (3.4)	9 (2.0)	1.8 (0.6-5.4)
Major birth defects in the retinoids group:			
n = 1, *congenital cerebral cysts (newborn with autism)*			
n = 1, *bilateral polycystic kidneys (early termination of pregnancy at 21 weeks)*			
n = 1, *hemangiomas (all body)*			
n = 1, *angiomas (feet and back)*			
n = 1, *congenital cataract (right eye)*			
n = 1, *microphthalmia (right eye)*			
n = 1, *cleft soft palate*			
n = 1, *ventricular septal defect + congenital pulmonary valve stenosis + coarctation of aorta + undescended testicle*			
Minor birth defects, No. (%)	7 (3.0)	11 (2.5)	1.3 (0.4-3.7)
Minor birth defects in the retinoids group:			
n = 2, *ankyloglossia*			
n = 1, *ear lobe undeveloped*			
n = 1, *blurred vision (hypermetropia)*			
n = 1, *congenital nonneoplastic nevus*			
n = 1, *metatarsus varus*			
n = 1, *other misshapen ear (similar to mother's ears)*			

or according to standard algorithms for uncertain dates or discrepant ultrasound dating, was similar in both groups (mean [SD], 39.4 [1.9] vs 39.4 [2.1] weeks; $P = .43$). The proportion of preterm infants (<37 completed weeks' gestation) did not significantly differ between study groups (5% for the retinoids group vs 7% for the control group; $P = .32$). No statistical difference in birth weight was detected ($P = .32$).

Eight major and 7 minor birth defects among liveborn infants were observed in the retinoids group compared with 9 and 11, respectively, in the control group (Table V). One of the major birth defects (ie, bilateral polycystic kidneys) was diagnosed at week 21 of pregnancy and led to therapeutic termination. Other than this case, no elective termination or spontaneous abortion is known to have been motivated or shown by a major malformation. However, no systematic histopathologic investigation was conducted. There were no significant differences between the exposed and control groups in the occurrence of major birth defects (OR [CI], 1.8 [0.6-5.4]) and minor birth defects (1.3 [0.4-3.7]). Furthermore, none of the children showed features of retinoid embryopathy in the retinoids group.

Based on 235 topical retinoid exposures and 444 controls, our study had sufficient power (80%) to detect a 2.4 increase in the risk for major birth defects and a 2.5 increase for minor birth defects ($\alpha = 0.05$ and $\beta = 0.2$).

DISCUSSION

To our knowledge, this is the largest prospective cohort study on reproductive safety of topical retinoids during pregnancy. Consistent with previously published epidemiologic observations, we found no significant differences in infants exposed to topical retinoids compared with controls on any outcome measured, except for elective pregnancy termination. Furthermore, we found no evidence of an increase in anomalies consistent with retinoic acid embryopathy.

Our findings are also consistent with the lack of biological plausibility for a teratogenic effect due to limited systemic bioavailability of retinoids applied by the transdermal route.[6,26] Although appropriate levels of retinol must be maintained for normal embryogenesis, both deficiencies and excess levels may be teratogenic. The exogenous application of topical retinoids is not expected to significantly increase endogenous levels. A physiologically based pharmacokinetic evaluation of topical retinoids predicted that

systemic exposure to tretinoin through the skin results in a 4 to 5 order of magnitude lower exposure than a minimally teratogenic dose.[5] Furthermore, the results of various studies on the systemic absorption of retinoids after topical use suggest very low plasmatic levels. Neither single-dose nor long-term treatment with topical 0.05% tretinoin cream affected endogenous levels of tretinoin or its metabolites.[7] After 42 days of an excessive application of 0.1% isotretinoin cream, plasma concentrations indicated systemic absorption but to a lesser extent than reported after oral intake of 5000 IU of vitamin A supplementation.[27] After topical treatment of the entire facial area with adapalene 0.1% gel once daily for 12 weeks, no adapalene could be detected in the plasma of exposed patients.[28] The systematic bioavailability of tazarotene nears 1% of the dose after single or multiple applications to healthy skin but might increase up to 5% under steady-state conditions in patients with psoriasis.[8] In summary, under usual therapeutic use conditions, an increase in plasma concentration resulting from topical retinoid application is expected to be far less than naturally occurring (endogenous) retinoid plasma levels.

Several case reports of malformations compatible with retinoid embryopathy after maternal use of topical tretinoin during the first trimester of pregnancy nevertheless have been published.[11-15] Although it is certainly possible that these associations were coincidental, a specific individual susceptibility to the risk of embryopathy from topical retinoids use cannot be completely ruled out.

The increased number of elective terminations of pregnancy after inadvertent exposure to topical retinoids could not be attributed directly as a cause for elective termination of pregnancy, as information on factors influencing the patient's decision to terminate pregnancy was not reported. However, it is possible that patients' or providers' perceptions of fetal risk might have contributed to this eventuality. Since the thalidomide disaster, a high level of anxiety among patients and physicians has been observed regarding the use of drugs in general during pregnancy. For drugs associated with negative outcomes, this anxiety can even become deleterious. Thus, doubts on the safety of a drug can lead to potential harmful effects such as psychological distress, abrupt discontinuation of needed medication, and even termination of healthy and otherwise wanted pregnancies.[29,30]

In our study, different retinoids were pooled together for the statistical analysis. Different compounds, however, may have a different teratogenic potential, depending on their pharmacotoxicological activity or susceptibility to absorption in the systemic circulation. The impact of this heterogeneity on primary end points was explored by logistic regression analysis, and no effect was observed.

It is well known that the prevalence of congenital malformations is linked to maternal age. Yet, the difference observed (32 vs 30 years) is not expected to significantly change the prevalence of overall congenital birth defects according to previous findings.[31] This was confirmed by a regression analysis that indicated that the slight age difference reported in our study had no impact on the major and minor birth defect rates (results not shown).

The limitations of this study involve in particular the relatively small sample size, despite data collected over 10 years and the contribution of 11 TIS centers. Based on 235 topical retinoid exposure cases, our study had the power to detect a 2 to 3 times increase in the risk of birth defects. Loureiro et al[17] calculated that their sample size (N = 106) was sufficient to rule out a 4-fold risk for all major structural defects combined. Even if the absence of features compatible with retinoid embryopathy is clearly reassuring, smaller effects may not have been detected. Thus, it is important that more research is conducted to increase sample size and allow for detection of infrequent outcomes. Although the response rate was not 100%, it is important to note that the rate of loss to follow-up is expected to be the same in the exposed group and control group as the cases lost to follow-up are mostly due to technical reasons (eg, change of address), which should randomly occur, and not because of a refusal to fill in the questionnaire. We therefore believe that this does not introduce a significant selection bias. Another limitation was that some factors considered potential confounders were not fully documented (ie, street drug use, concomitant medication, gestity, parity, social status) for analysis. The effects of potent teratogens are likely to outweigh concerns surrounding adjustment for confounders. Additional data on potential confounders, however, would contribute to quantify moderate increases in risk. Teratogen information services are likely to provide the most accurate information because most cases are reviewed by an expert in teratology, and the reporter is usually the obstetrician attending the birth. Such centers encourage follow-up by minimizing the effort for the physician in terms of paperwork and time, though, thus leading to a lack of completeness of outcome data. Finally, other limitations of the study are as follows: recruitment not early enough to assess risk for early first-trimester miscarriage; reliance on maternal interview as a source for outcome data in a large proportion of

cases; variation in timing of follow-up; combining data from 11 TIS, including 3 centers without control data (a subanalysis showed no significant difference on primary end points); and a nonrandomized design with no blindness to exposure. However, applying the same procedure to both groups and the prospective nature of data collected minimize potential biases (eg, no significant difference on primary end points observed between recruitment centers; $P = .8$ for major birth defects and $P = .1$ for minor birth defects). Although not ideal compared with prospective, randomized control trials, such epidemiological surveys have the advantage of easier feasibility and the merit of providing rapidly useful information.

In summary, women exposed to topical retinoids during the first trimester of pregnancy do not seem at higher risk for major birth defects in neonates, above the baseline rate of 1% to 3%. Furthermore, this study found no evidence of an increase in anomalies consistent with retinoic acid embryopathy. This evidence-based information can be helpful to women and health care professionals who are facing a pregnancy diagnosis after maternal exposure to topical retinoids. These results, together with the previous epidemiologic observations, allow for reassurance in cases of inadvertent exposure during pregnancy. However, according to the current knowledge, topical retinoids certainly cannot be advised for use during pregnancy, as their risk/benefit ratio remains uncertain.

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REFERENCES

1. Lammer EJ, Schunior A, Hayes AM, et al. Isotretinoin dose and teratogenicity. *Lancet*. 1988;2(8609):503-504.

2. Adams J, Lammer EJ. Neurobehavioral teratology of isotretinoin. *Reprod Toxicol*. 1993;7(2):175-177.

3. US Food and Drug Administration. iPLEDGE. http://www.fda.gov/Drugs/DrugSafety/Postmarket DrugSafety Informationfor PatientsandProviders/ucm094305.htm. Accessed July 14, 2011.

4. De Santis M, Straface G, Cavaliere A, et al. The need for restricted prescription of retinoic acid derivative isotretinoin to prevent retinoid teratogenicity. *Prev Med*. 2007;45(2-3):243-244.

5. Clewell HJ, Andersen ME, Wills RJ, et al. A physiologically based pharmacokinetic model for retinoic acid and its metabolites. *J Am Acad Dermatol*. 1997;36(3, pt 2):S77-S85.

6. Jensen BK, McGann LA, Kachevsky V, et al. The negligible systemic availability of retinoids with multiple and excessive topical application of isotretinoin 0.05% gel (Isotrex) in patients with acne vulgaris. *J Am Acad Dermatol*. 1991;24(3):425-428.

7. Latriano L, Tzimas G, Wong F, et al. The percutaneous absorption of topically applied tretinoin and its effect on endogenous concentrations of tretinoin and its metabolites after single doses or long-term use. *J Am Acad Dermatol*. 1997;36(3, pt 2):S37-S46.

8. Tang-Liu DD, Matsumoto RM, Usansky JI. Clinical pharmacokinetics and drug metabolism of tazarotene: a novel topical treatment for acne and psoriasis. *Clin Pharmacokinet*. 1999;37(4):273-287.

9. Van Hoogdalem EJ, Baven TL, Spiegel-Melsen I, et al. Transdermal absorption of clindamycin and tretinoin from topically applied anti-acne formulations in man. *Biopharm Drug Dispos*. 1998;19(9):563-569.

10. Willhite CC, Sharma RP, Allen PV, et al. Percutaneous retinoid absorption and embryotoxicity. *J Invest Dermatol*. 1990;95(5):523-529.

11. Camera G, Pregliasco P. Ear malformation in baby born to mother using tretinoin cream. *Lancet*. 1992;339(8794):687.

12. Colley SM, Walpole I, Fabian VA, et al. Topical tretinoin and fetal malformations. *Med J Aust*. 1998;168(9):467.

13. Lipson AH, Collins F, Webster WS. Multiple congenital defects associated with maternal use of topical tretinoin. *Lancet*. 1993;341(8856):1352-1353.

14. Navarre-Belhassen C, Blanchet P, Hillaire-Buys D, et al. Multiple congenital malformations associated with topical tretinoin. *Ann Pharmacother*. 1998;32(4):505-506.

15. Selcen D, Seidman S, Nigro MA. Otocerebral anomalies associated with topical tretinoin use. *Brain Dev*. 2000;22(4):218-220.

16. Jick SS, Terris BZ, Jick H. First trimester topical tretinoin and congenital disorders. *Lancet*. 1993;341(8854):1181-1182.

17. Loureiro KD, Kao KK, Jones KL, et al. Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children of women exposed to topical tretinoin during early pregnancy. *Am J Med Genet A*. 2005;136(2):117-121.

18. Shapiro L, Pastuszak A, Curto G, et al. Safety of first-trimester exposure to topical tretinoin: prospective cohort study. *Lancet*. 1997;350(9085):1143-1144.

19. Autret E, Berjot M, Jonville-Bera AP, et al. Anophthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy. *Lancet*. 1997;350(9074):339.

20. Carlier P, Choulika S, Dally S. Topical retinoids exposure in pregnancy. *Thérapie*. 1998;53:180.

21. Martinez-Frias ML, Rodriguez-Pinilla E. First-trimester exposure to topical tretinoin: its safety is not warranted. *Teratology*. 1999;60(1):5.

22. Bozzo P, Chua-Gocheco A, Einarson A. Safety of skin care products during pregnancy. *Can Fam Physician*. 2011;57(6):665-667.

23. Schaefer C, Hannemann D, Meister R. Post-marketing surveillance system for drugs in pregnancy: 15 years experience of ENTIS. *Reprod Toxicol*. 2005;20(3):331-343.

24. Clementi M, Di Gianantonio E, Ornoy A. Teratology information services in Europe and their contribution to the prevention of congenital anomalies. *Community Genet*. 2002;5(1):8-12.

25. Rasmussen SA, Olney RS, Holmes LB, et al. Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Res A Clin Mol Teratol*. 2003;67(3):193-201.

26. Buchan P, Eckhoff C, Caron D, et al. Repeated topical administration of all-trans-retinoic acid and plasma levels of retinoic acids in humans. *J Am Acad Dermatol*. 1994;30(3):428-434.

27. Chen C, Jensen BK, Mistry G, et al. Negligible systemic absorption of topical isotretinoin cream: implications for teratogenicity. *J Clin Pharmacol*. 1997;37(4):279-284.

28. Shalita A, Weiss JS, Chalker DK, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. *J Am Acad Dermatol*. 1996;34(3):482-485.

29. Koren G, Bologa M, Long D, et al. Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. *Am J Obstet Gynecol*. 1989;160(5, pt 1): 1190-1194.

30. Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. *Eur J Clin Pharmacol*. 2010;66(2):207-214.

31. Croen LA, Shaw GM. Young maternal age and congenital malformations: a population-based study. *Am J Public Health*. 1995;85(5): 710-713.